IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant(s): COHEN, Luba

Application No.: Group:

Filed: September 20, 2001 Examiner:

For: LICORICE EXTRACT FOR USE AS MEDICAMENT

L E T T E R

Assistant Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

September 20, 2001
2786-0191P

Sir:

Under the provisions of 35 USC 119 and 37 CFR 1.55(a), the applicant hereby claims the right of priority based on the following application(s):

Country	Application No.	Filed
Israel	138603	09/21/00

A certified copy of the above-noted application(s) is(are) attached hereto.

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Respectfully submitted,

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BSLB 703-205-8000
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September 20, 2001
1 of 1

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משרד המשפטים
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This 09 -09- 2001 היום

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רשם הפטנטים
Commissioner of Patents

נתאשר
Certified

חוק הפטנטים, תשכ"ז – 1967
PATENTS LAW, 5727-1967

בקשה לפטנט
Application For Patent

לשימוש הלשכה
For Office Use

מספר: Number	130603
תאריך: Date	21-09-2000
הוקדם/נדחה: Ante/Post-dated	

אני, (שם המבקש, מענו ולגבי גוף מאוגד ת מקום התאגדותו)
I, (Name and address of applicant, and in case of body corporate-place of incorporation)

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בעל אמצאה מכח הדין
Owner, by virtue of Right of Law

ששמה הוא
of an invention the title of which is

(בעברית)
(Hebrew)

מיצוי ליקוריס לשימוש כתרופה

(באנגלית)
(English)

Licorice extract for use as a medicament

מבקש בזאת כי ינתן לי עליה פטנט
Hereby apply for a patent to be granted to me in respect thereof.

* בקשת חלוקה Application of Division	* בקשת פטנט מוסף Appl. for Patent of Addition
מבקשת פטנט from application	* לבקשה/לפטנט to Patent/Appl.
No. מס'	No. מס'
Dated מיום	Dated מיום

* יפוי כח: P.o.A.:
עוד יוגש

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Signature of Applicant

For the Applicants,
REINHOLD COHN AND PARTNERS
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דרישת דין קדימה*
Priority Claim

מדינת האיגוד Convention Country	תאריך Date	מספר/סימן Number/Mark

היום This 20 בחודש of September שנת Year 2000

לשימוש הלשכה
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מיצוי ליקוריס לשימוש כתרופה

Licorice extract for use as a medicament

Ready-Made 37 (1999) Ltd

רדי-מייד 37 (1999) בע"מ

C. 123927

LICORICE EXTRACT FOR USE AS A MEDICAMENT

FIELD OF THE INVENTION

This invention relates to pharmaceutical and nutraceutical compositions that contain licorice extract.

BACKGROUND OF THE INVENTION

Licorice roots, which consist of the dried unpeeled roots of Glycyrrhiza are widely used in Asia as a sweetener and a spice. Licorice root has also been used medically for more than 3000 years, and a wide range of therapeutic uses have been ascribed thereto. Glycyrrhizinic acid, contained in licorice root, was attributed several pharmacological activities, such as anti-bacterial, anti-viral, anti-inflammatory, anti-allergic and anti-hepatotoxic activity. However, the traditional licorice extracts, and in particular glycyrrhizinic acid, were also shown to cause hypertension, and this severe side effect considerably reduced their use.

Recently, Fuhrman et al. showed that a certain ethanolic extract of licorice is useful in inhibition of LDL oxidation. [Fuhrman et al., The American Journal of Clinical Nutrition, 66, pp. 267-75 (1997)]. This very same study, however, did not find that the consumption of that licorice extract by humans causes any significant influence on plasma cholesterol, LDL concentration, or any other medical characteristic examined.

SUMMARY OF THE INVENTION

The present invention is based on the finding that a licorice extract similar to that used by Fuhrman et al. is useful in decreasing in human subjects the blood

pressure, blood glucose concentration, blood total cholesterol and LDL levels, and blood trygliceride and VLDL concentration. Other findings that led to the present invention are that licorice extract consumption reduces the susceptibility of human blood serum LDL to two heterogenic modifications, namely: retention and aggregation. The licorice extract that was found to bring to these results is characterized by being water-insoluble and free from glycyrrhizinic acid.

In the following, blood pressure, blood cholesterol and LDL levels, blood trygliceride and VLDL concentration, blood glucose concentration, and serum LDL susceptibility to retention and aggregation will be named generally "risk factors", since they are related to the risk of cardiovascular diseases.

Thus, the present invention provides a pharmaceutical or neutraceutical preparation for lowering at least one of the following risk factors: blood pressure, glucose concentration, blood cholesterol and LDL levels, blood trygliceride and VLDL concentration, and serum LDL susceptibility to retention and aggregation, said preparation comprising licorice extract, which is water-insoluble and free from glycyrrhizinic acid.

Preferably, the pharmaceutical or neutraceutical composition of the invention is for lowering at least one of the following risk factors: blood pressure, blood glucose concentration, susceptibility of serum LDL to retention, and susceptibility of serum LDL to aggregation.

Most preferably the pharmaceutical or neutraceutical composition of the present invention is for lowering at least one of the following risk factors: blood pressure and glucose concentration.

According to another aspect, the present invention provides licorice extract, which is water-insoluble and free from glycyrrhizinic acid, for use in the prevention and/or treatment of at least one of the following conditions and diseases: inflammation, hypertension, diabetes, chronic renal failure, atherosclerotic diseases, carotid artery stenosis, coronary heart diseases, hypercholesterolemia, and hypertriglyceridemia.

Preferably, the use according to the invention is in the prevention and/or treatment of at least one of the following conditions: hypertension, diabetes, chronic renal failure, and inflammation.

The term *prevention* means reduction of the risk of having the condition or the disease, while the term *treatment* means slowing down the development of the condition or the disease or relieving at least one symptom thereof.

The invention also provides the use of licorice extract, which is free from glycyrrhizinic acid, in the preparation of a medicament for preventing or treating any of the conditions and diseases mentioned above.

The invention also provides a pharmaceutical or neutraceutical immuno-potentiator comprising a licorice extract, which is water-insoluble and free from glycyrrhizinic acid. The immuno-potentiating value of the extract may be deduced from its ability to reduce the susceptibility of human serum to LDL aggregation.

According to another aspect of the present invention there is provided a method for treating hypertension, diabetes, chronic renal failure, cardiovascular diseases, carotid artery stenosis, atherosclerotic diseases, and coronary heart diseases in a subject, comprising administering to said subject a therapeutically effective amount of a licorice extract that is water-insoluble and free of glycyrrhizinic acid.

Preferably, the method of the invention is for treating hypertension, diabetes, and chronic renal failure, and most preferably hypertension.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, a detailed description of some experimental results will now be given, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 is a graph showing the effect of licorice extract on systolic blood pressure;

Fig. 2 is a graph showing the effect of licorice extract on diastolic blood pressure;

Fig. 3 is a graph showing the effect of licorice extract on cholesterol levels in the blood;

Fig. 4 is a graph showing the effect of licorice extract on LDL levels in the blood;

Fig. 5 is a graph showing the effect of licorice extract on HDL levels in the blood;

Fig. 6 is a graph showing the effect of licorice extract on VLDL levels in the blood;

Fig. 7 is a graph showing the effect of licorice extract on triglycerides levels in the blood;

Fig. 8 is a graph showing the effect of licorice extract on glucose levels in the blood.

Fig. 9 is a graph showing the effect of licorice extract on serum susceptibility to LDL retention.

Fig. 10 is a graph showing the effect of licorice extract on serum susceptibility to LDL aggregation.

DETAILED DESCRIPTION OF THE INVENTION

1 kg raw Licorice root was ground to obtain slices of about 0.5 to 2 cm length and dried. The dry ground root was steeped in 5 liter absolute ethanol at room temperature, stirred for 5 hours, and filtered. The ethanol was evaporated and the resultant residue was dried to constant mass at 85°C to give 30 gr of product.

The product, hereinafter referred to as *licorice extract*, was then pulverized to give fine reddish brown powder that is practically insoluble in water and with no traceable amount of glycyrrhizinic acid. The powder was conventionally encapsulated and given to the volunteers in the experiment described bellow.

Some notes on the above procedure are in place: licorice extracts of similar health promoting effects, even if in other concentrations and required dosages, may be obtained also with other extracting solutions like acetone, ethyl acetate or hexane. Ethanol was found by the inventors to give the extract with the highest yield and activity. In any case, it is important that the raw material is dried before the extraction and that the extraction is carried out in a dry solvent. Otherwise, the product will be somewhat water-soluble, and obtaining the extract of the invention will necessitate expensive and complicated processes for removing the water-soluble portions of the extract.

Twelve adult hypercholesterolemic patients consumed for one month 100mg licorice extract per day. The risk factors defined above were measured in these patients before and after licorice consumption, and compared. The results are shown in Figures 1 to 10.

In Figures 1 to 8 and 10 the X axis values are of the measured risk factor before licorice consumption, the Y axis values are of the measured risk factor after licorice consumption, and the straight line is the equation Y=X. Every point bellow this line represents (at least one) patient in whom the measured risk factor after licorice consumption was lower then before.

Fig. 1 shows that ten out of the twelve patients showed a decrease in the systolic blood pressure after licorice consumption. **Fig. 2** shows that the diastolic blood pressure of the same 12 patients was not significantly effected by the licorice consumption.

Lowering the blood pressure may be useful in reducing the risk to atherosclerotic diseases and is desirable in the treatment of a variety of disease and

conditions, e.g. cardiovascular diseases, chronic renal failure, carotid artery stenosis, and coronary heart diseases, in patients with high blood pressure.

The graphs in **Figs. 3** and **4** show the cholesterol and LDL levels (measured in mg/dl) in the same patients before and after consuming licorice extract. As shown in the figures, after consumption of licorice extract the cholesterol level decreased in 10 out of 12 patients and the LDL decreased in 11 out of 12. **Fig. 5** shows that no significant change of HDL levels was detected after consumption of the licorice extract. As may be deduced from the results shown in **Figs. 3, 4**, and 5 most of the decrease in cholesterol is due to a decrease in the LDL level, not in HDL level. Lowering the cholesterol and LDL levels may effect hypercholesterolemic patients to reduce the risk of atherosclerotic diseases and is desirable in the treatment of cardiovascular diseases, chronic renal failure, carotid artery stenosis, and coronary heart diseases in these patients. The simultaneous lowering of the LDL levels and blood pressure that the licorice extract exhibits may be especially beneficial to patients that suffer from both high blood pressure and high LDL levels. On the other hand it makes the licorice extract effective to a wide population, including both hypertension and hypercholesterolemic patients.

Figs. 6 and 7show that after the licorice consumption, all the twelve patients had lower blood concentration of triglycerides than they had prior to this consumption, and 10 out of 12 had lower VLDL blood concentration. Furthermore, the average decrease in the triglycerides level was about 20%, which is remarkable for one month treatment. Lowering the triglycerides and the VLDL concentrations may have beneficial effects as were already mentioned before, and widens even more the population that may benefit from licorice extract consumption. It may also be useful as a single medication to help people that suffer from more than one of the risk factors: high blood pressure, high cholesterol and LDL levels, and high triglyceride concentration.

Fig. 8 shows the effect of licorice extract on blood-glucose. The figure shows that in 10 out of the twelve patients the blood-glucose decreased. Lowering the blood-glucose may reduce the risk to diabetes and its complications, including,

for instance, chronic renal failure, blindness, and acceleration of atherosclerotic processes. The combination of lowering the glucose levels in the blood and lowering the blood pressure may be most beneficial to patients that are at high risk to renal failure. The combination of these two effects with the lowering of cholesterol and LDL levels may be beneficial to patients that suffer from any combination of the four risk factors.

Fig. 9 is a graph of the development of serum-LDL optical density at 680nm during vortexing at a constant strength before licorice consumption, after licorice consumption, and after placebo consumption. The placebo was given for one month after the consumption of the licorice extract. The graph clearly shows that the LDL susceptibility to aggregation was lowered by the licorice consumption and returned to baseline level after licorice intact termination and placebo consumption.

Figure 10 shows the effect of licorice extract consumption on LDL retention. The results clearly show the LDL retention was significantly lowered thanks to the licorice extract consumption.

CLAIMS:

1. A pharmaceutical or neutraceutical preparation for lowering in human patients at least one of the following risk factors: blood pressure, blood glucose concentration, LDL susceptibility to retention, LDL susceptibility to aggregation, blood total cholesterol and LDL levels, and blood tryglicerides and VLDL concentration, said preparation comprising licorice extract which is water-insoluble and free from glycyrrhizinic acid.

2. A pharmaceutical or neutraceutical preparation according to claim 1 for lowering at least one of the following risk factors: blood pressure, blood glucose concentration, serum LDL susceptibility to aggregation and serum LDL susceptibility to retention.

3. A pharmaceutical or neutraceutical preparation according to claim 1 for lowering blood pressure and/or glucose concentration.

4. A pharmaceutical or neutraceutical preparation according to claim 1 for lowering LDL susceptibility to aggregation and LDL susceptibility to retention.

5. A pharmaceutical or neutraceutical preparation according to claim 1 for lowering blood glucose concentration.

6. A pharmaceutical or neutraceutical preparation according to claim 1 for treating inflamation.

7. A pharmaceutical or neutraceutical preparation according to claim 1 for lowering at least two of the following risk factors: blood pressure, blood glucose concentration, LDL susceptibility to retention, LDL susceptibility to aggregation, blood total cholesterol and LDL levels, and blood tryglicerides and VLDL concentration.

8. A pharmaceutical or neutraceutical preparation according to claim 7 for lowering both blood tryglicerides and LDL levels without significantly decreasing the HDL level.

9. A pharmaceutical or neutraceutical preparation comprising licorice extract, which is water insoluble and free from glycyrrhizinic acid, for use in the prevention

and/or treatment of at least one of the following conditions and diseases: aterosclerotic diseases, hypertension, cardiovascular diseases, chronic renal failure, carotid artery stenosis, coronary heart diseases, hypercholesterolemia, and hypertriglyceridemia.

10. The use of a licorice extract, which is water-insoluble and free from glycyrrhizinic acid, in the preparation of a medicament for preventing and/or treating at least one of the following conditions and diseases: inflammation, hypertension, diabetes, chronic renal failure, atherosclerotic diseases, cardiovascular diseases, carotid artery stenosis, and coronary heart diseases.

11. The use of a licorice extract, which is water-insoluble and free from glycyrrhizinic acid, in the preparation of an immuno-potentiator.

12. A method for treating atherosclerotic diseases, hypertension, cardiovascular diseases, chronic renal failure, carotid artery stenosis, and coronary heart diseases in a subject, comprising administering to said subject a therapeutically effective amount of a licorice extract that is water-insoluble and free of glycyrrhizinic acid.

For the Applicants,
REINHOLD COHN AND PARTNERS
BY:

S. Hirsch

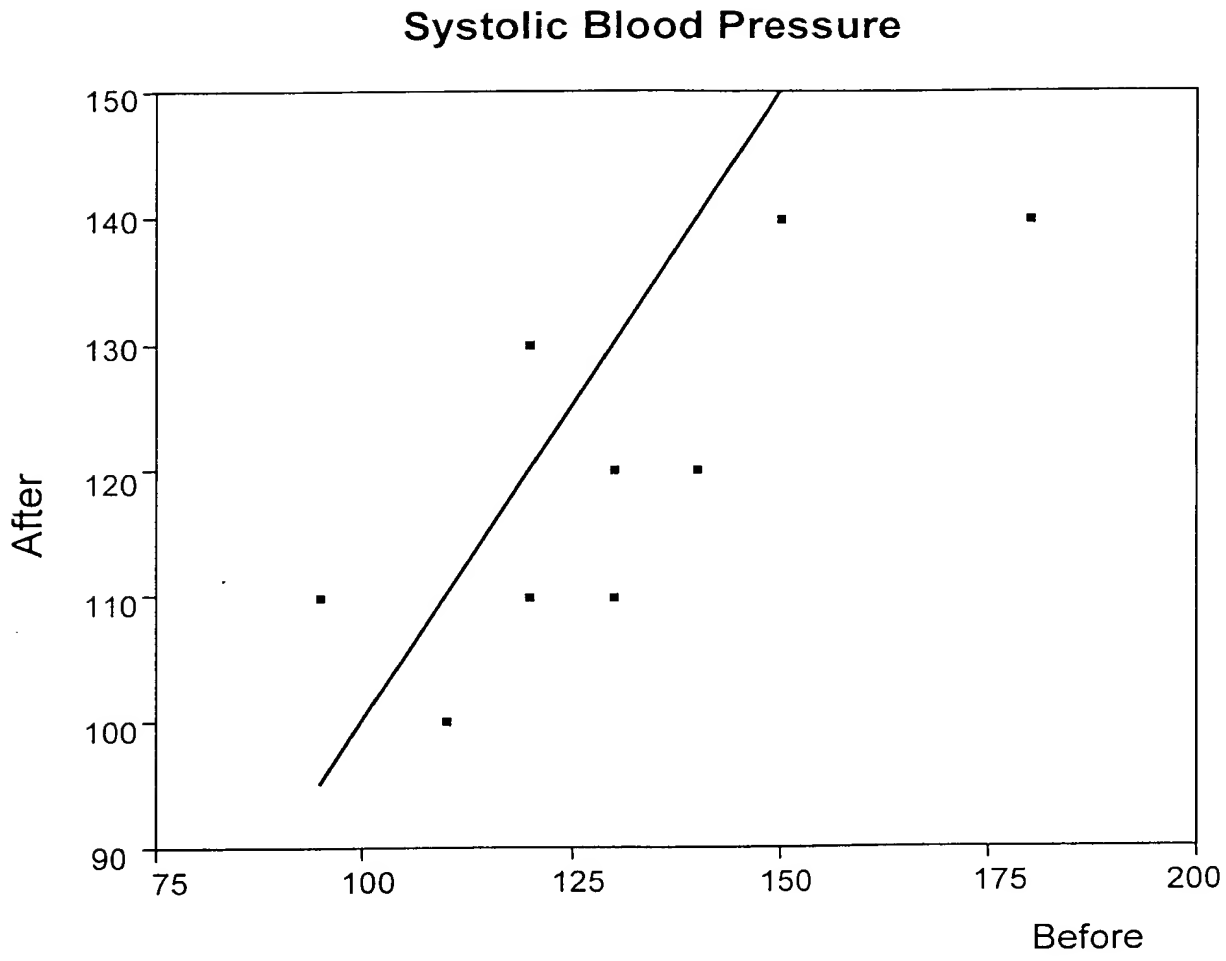
Systolic Blood Pressure
150
140
130
120
110
100
90
After
75
100
125
150
175
200
Before

FIG. 1

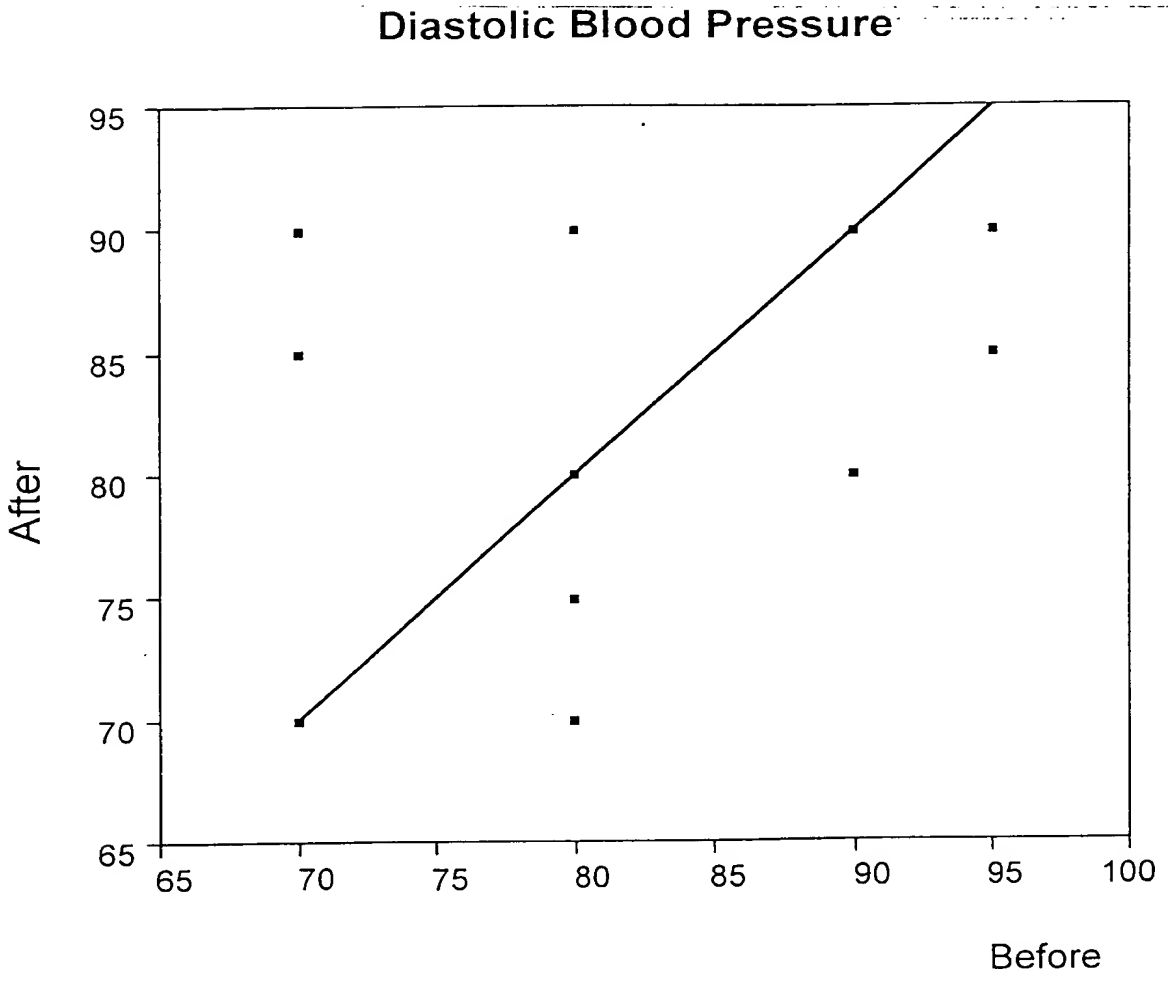
Diastolic Blood Pressure
After
95
90
85
80
75
70
65
65
70
75
80
85
90
95
100
Before

FIG. 2

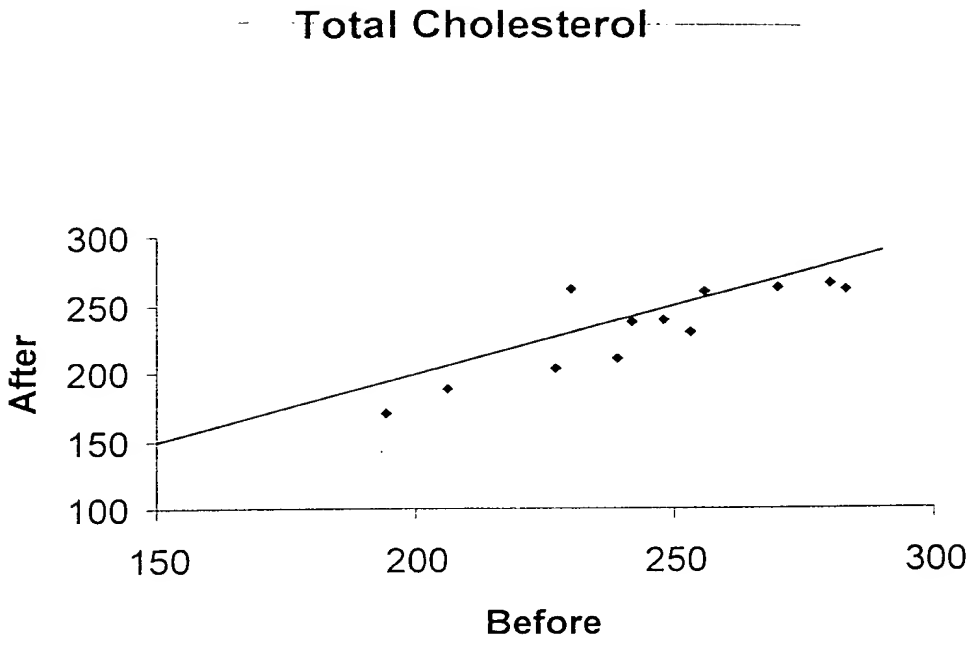
Total Cholesterol
After
300
250
200
150
100
150
200
250
300
Before

FIG. 3

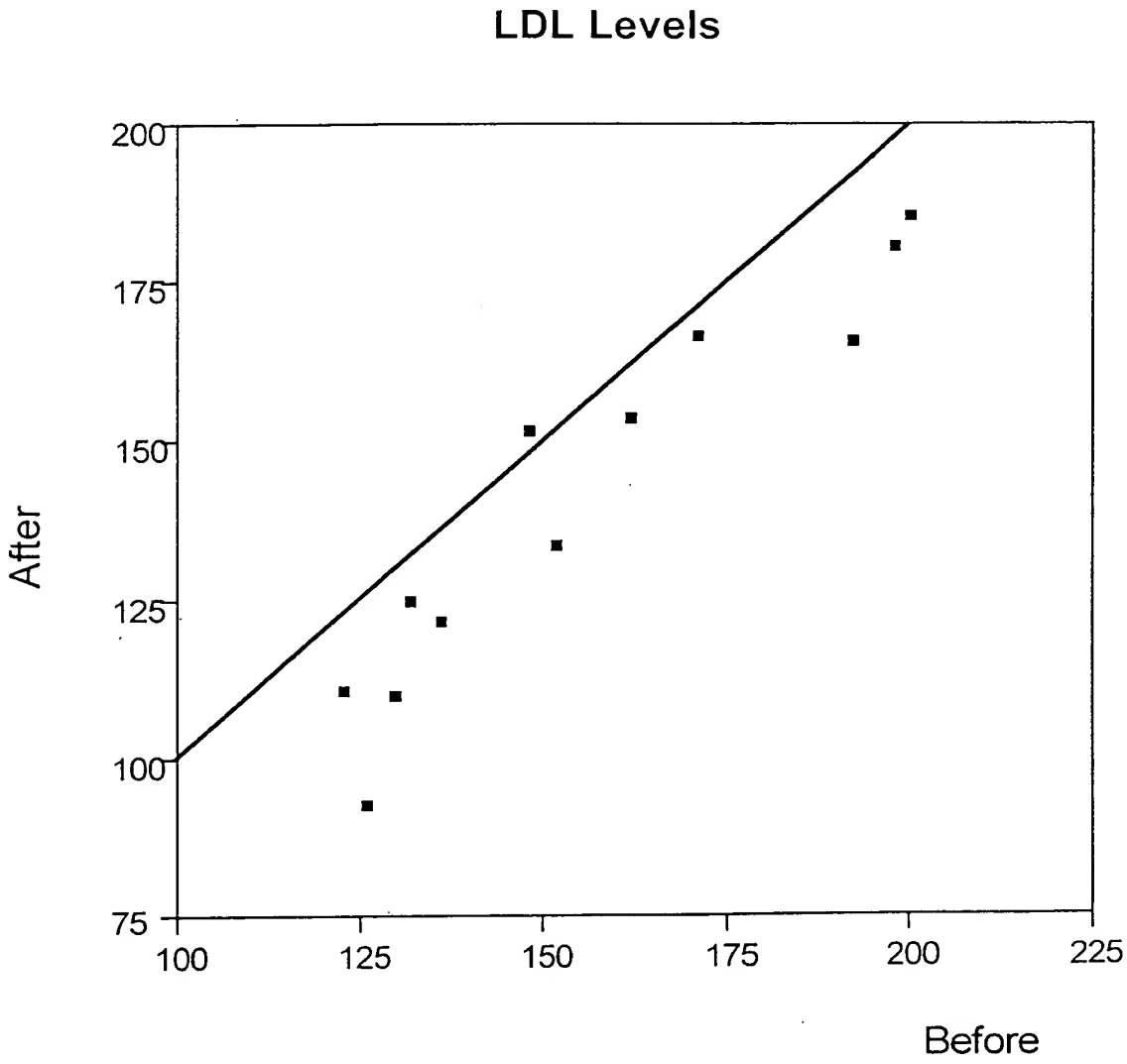
LDL Levels
200
175
150
125
100
75
After
100
125
150
175
200
225
Before

FIG. 4

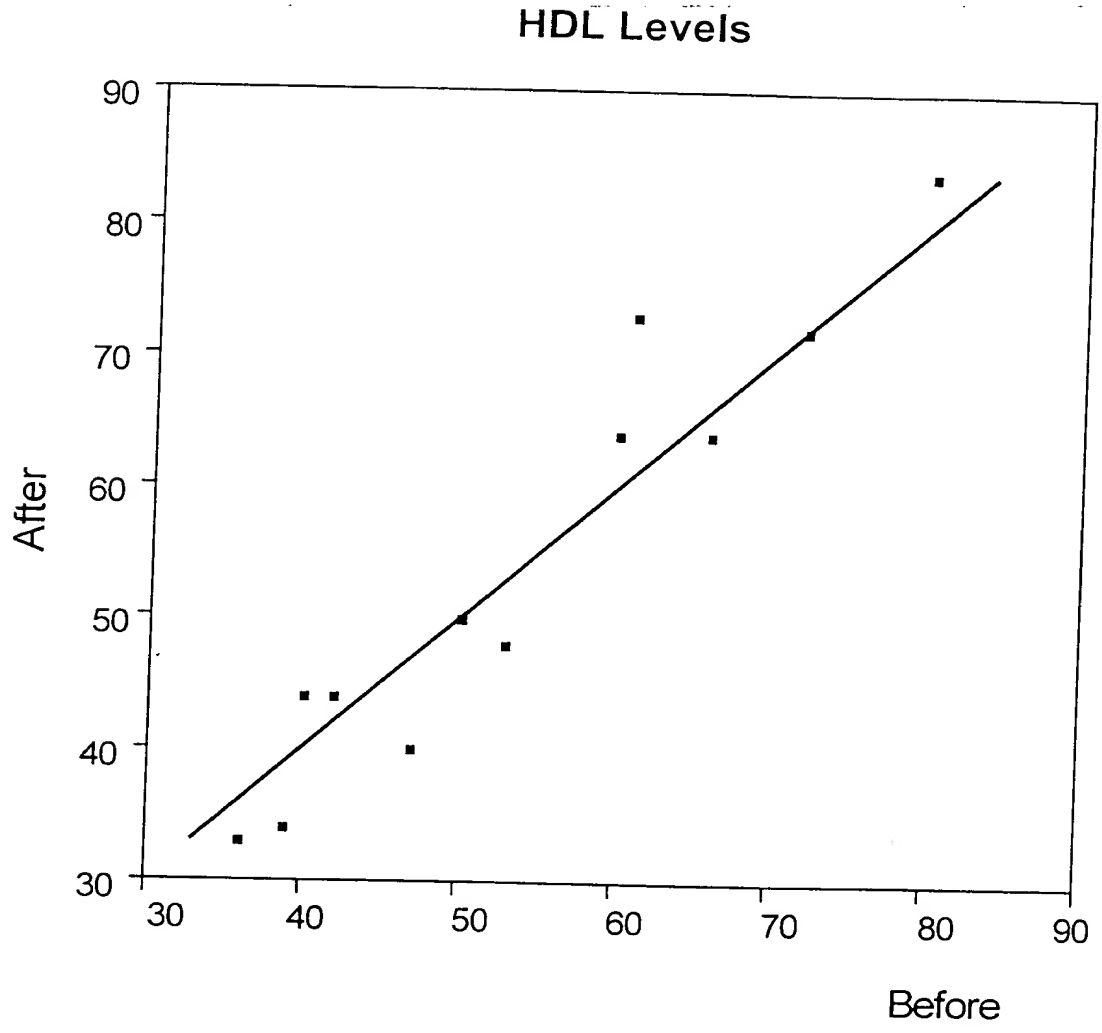

FIG. 5

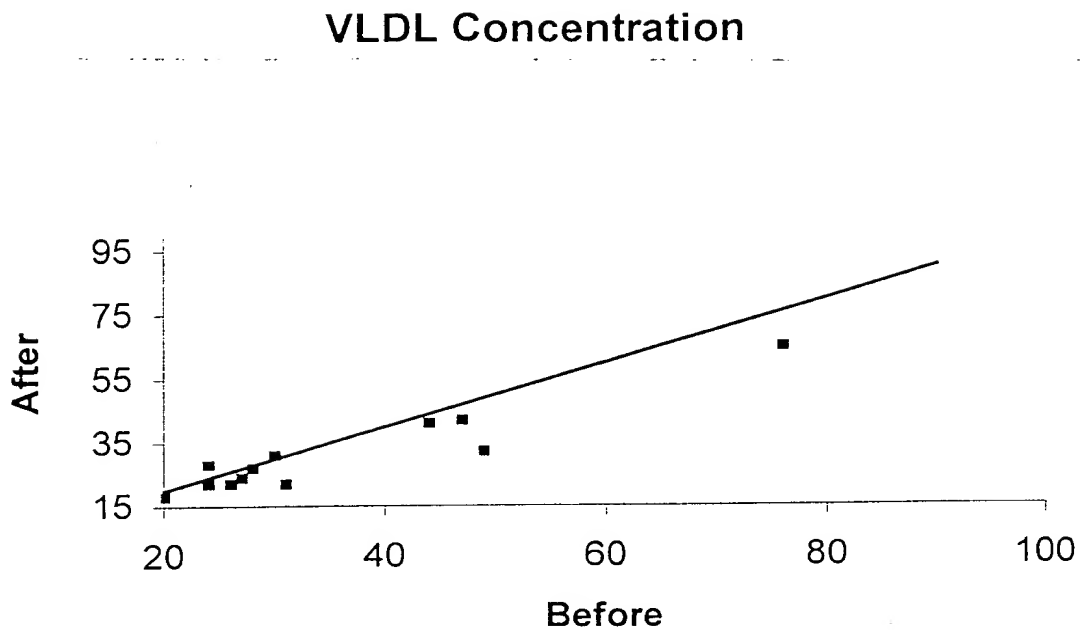

FIG. 6

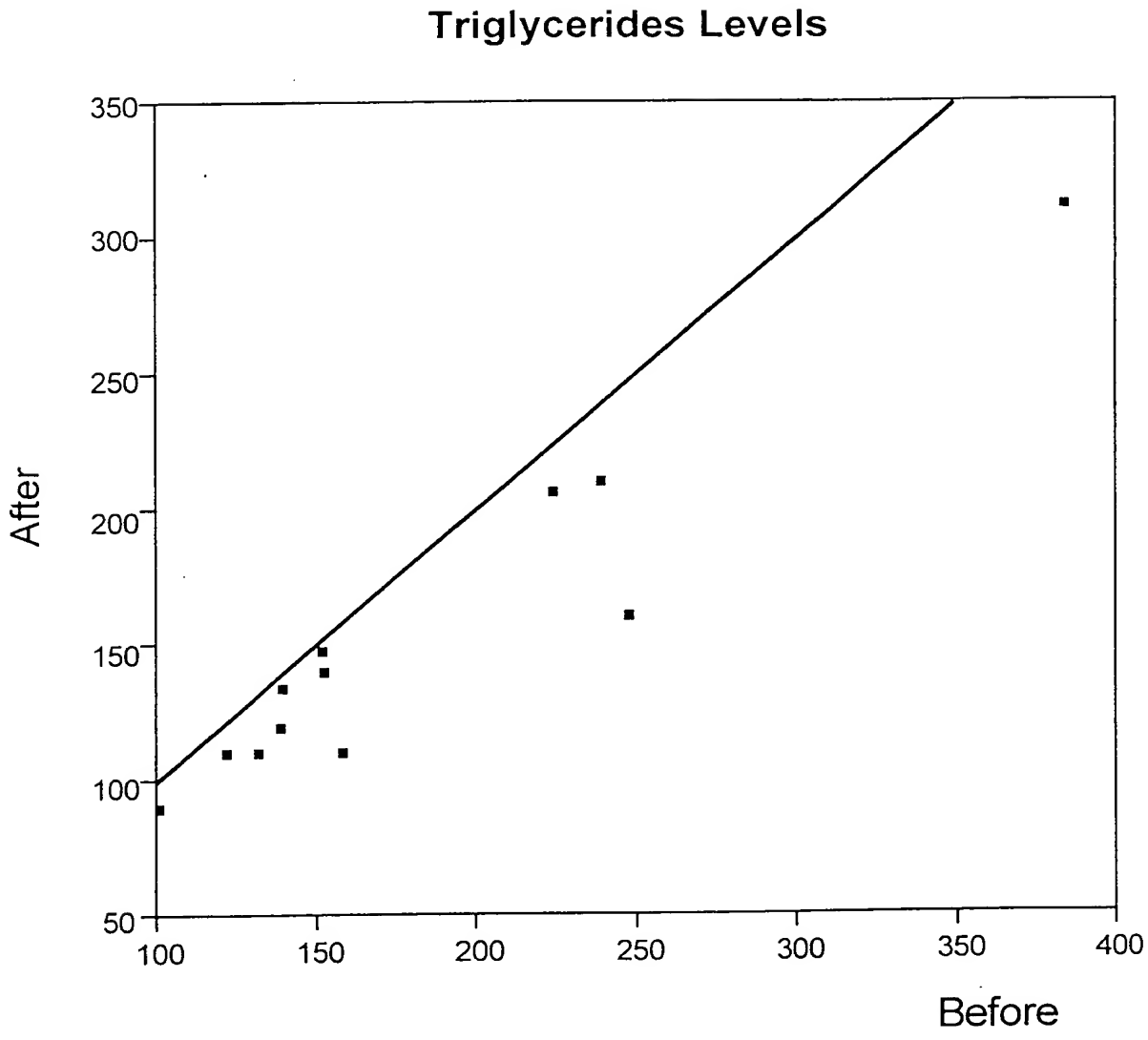
Triglycerides Levels
After
Before
350
300
250
200
150
100
50
100
150
200
250
300
350
400

FIG. 7

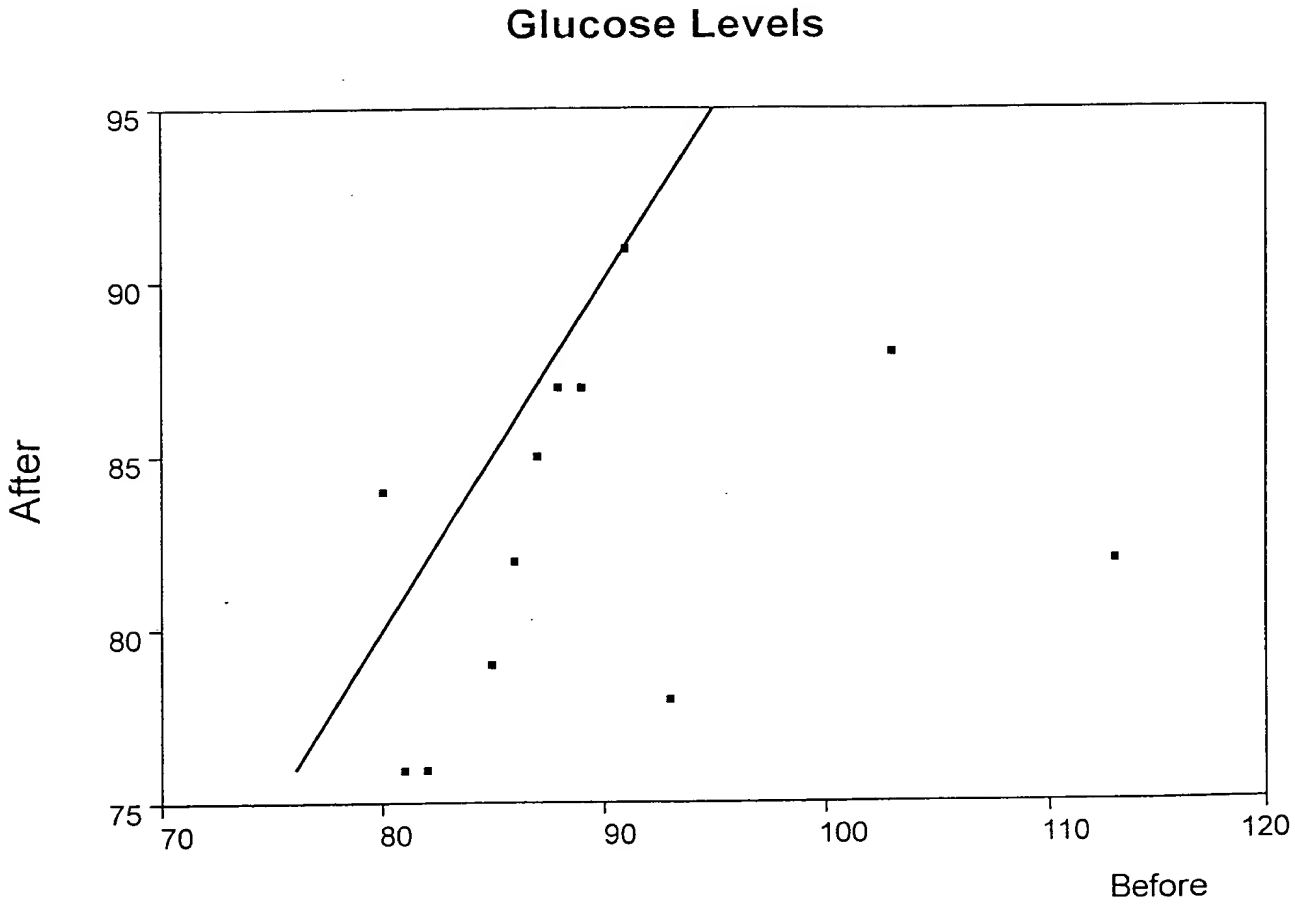

FIG. 8

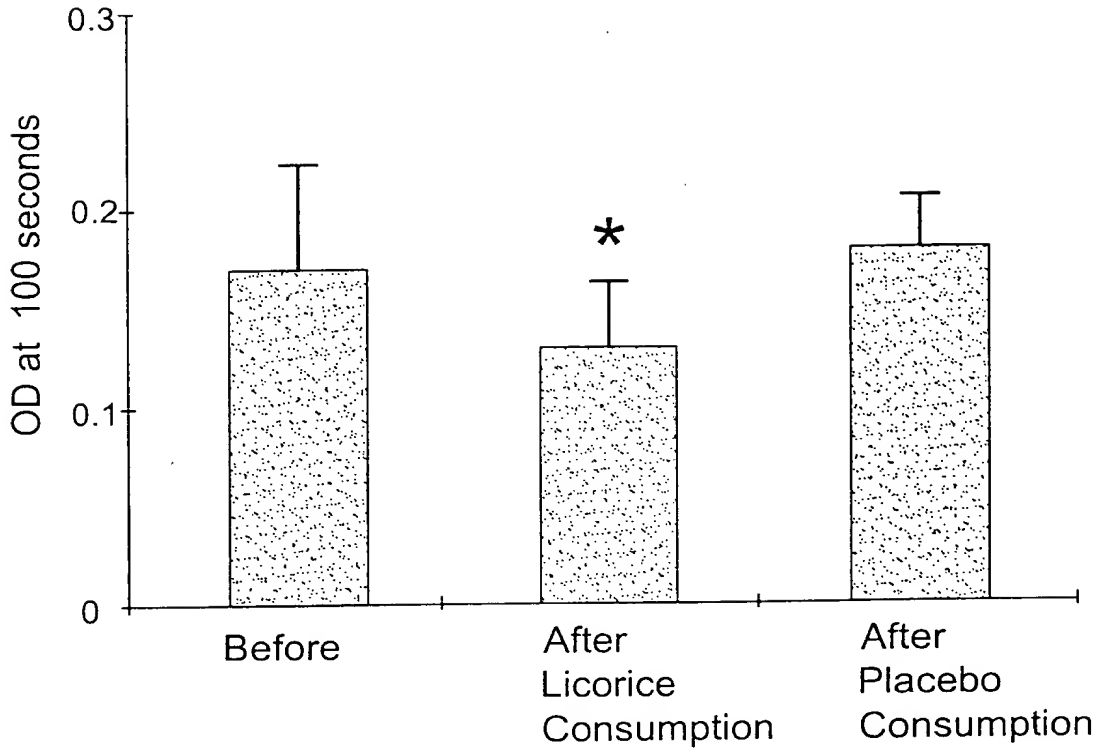
0.3
0.2
0.1
0
OD at 100 seconds
*
Before
After Licorice Consumption
After Placebo Consumption

FIG. 9

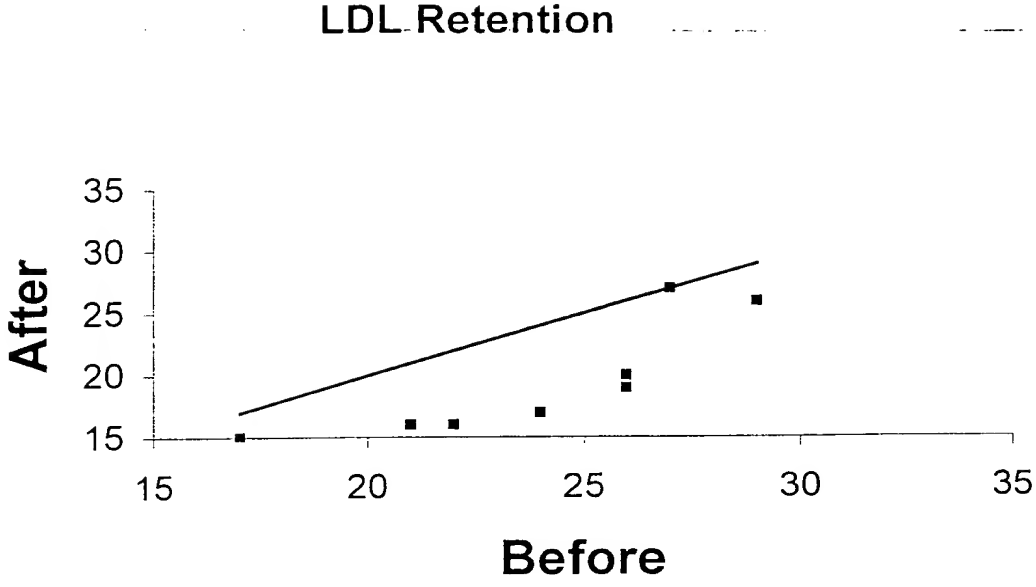

FIG. 10